STRESS VULNERABILITY AND ALCOHOL USE AND CONSEQUENCES: FROM HUMAN LABORATORY STUDIES TO CLINICAL OUTCOMES

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Abstract

It is well known that vulnerability to stress is a risk factor for alcohol use disorder (AUD). Chronic alcohol use can result in neuroadaptations in cortico-striatal pathways and hypothalamic pituitary adrenal (HPA) axis function that are manifested in altered behavioral and cognitive control functions contributing to alcohol craving, compulsive motivation, consumption and consequences. This symposium brings together studies utilizing novel approaches to help improve our understanding of stress – past, acute and chronic - on alcohol seeking and consumption and related outcomes using a combination of human laboratory models, neuroimaging and clinical measures. Examining factors that determine vulnerability as well as resilience to stress are of particular interest in the study of AUD because, in addition to increasing our understanding of the risk factors for AUD, such knowledge can be used to develop more effective treatments.

Dr. Stangl presented a novel human experimental model that demonstrates, for the first time, stress-induced increases in alcohol self-administration in binge drinkers using a guided imagery paradigm combined with intravenous alcohol self-administration (IV-ASA). Dr. Blaine presented data demonstrating that glucocorticoid response to stress drives compulsive alcohol motivation and intake in binge/heavy drinkers. Dr. Plawecki presented data examining sex differences in the effect of two distinct stress paradigms – mood induction and abstinence – on IV-ASA in moderate drinkers. Dr. Schwandt presented clinical data providing a new perspective on the relationship between childhood trauma and AUD by suggesting possible underlying mechanisms that confer resilience, rather than vulnerability, to severe early life stress exposure.

Introduction

The relationship between stress and alcohol is bi-directional and complex. It is well known that vulnerability to stress is a risk factor for alcohol use disorder (AUD). On the other hand, chronic alcohol use can result in neuroadaptations in stress-related brain pathways as well as in hypothalamic pituitary adrenal (HPA) axis function. These complex effects can be manifested in altered behavioral and cognitive control functions contributing to alcohol craving, compulsive motivation, consumption and consequences.

A pattern of excessive alcohol use following abstinence is a key element of alcohol addiction and is potently triggered by craving in response to stress and alcohol-associated stimuli (Sinha *et al*, 2011c). Studies have shown that craving responses to experimental stressors that mimic real-world relapse triggers (Monti *et al*, 1993; Sinha *et al*, 2009), as well as to alcohol cues, can predict relapse to alcohol use and abuse.(Seo *et al*, 2013; Sinha *et al*, 2011b). Additionally, exposure to early life adversity, including childhood trauma, has been repeated shown to have long-lasting impact on the body and brain, including increasing risk for developing alcohol use disorder (De Bellis and Zisk, 2014; Enoch, 2011; Schwandt *et al*, 2013). Stressful life events predict increased alcohol use in adolescents and young adults (Newcomb and Harlow, 1986; Wills, 1986) and exposure to adversity before the age of 18 is associated with incidence and persistence of alcohol use disorders (Green *et al*, 2010; Lloyd and Turner, 2008). Recent work has indicated a robust relationship between childhood trauma and greater prevalence of comorbid psychiatric conditions (Huang *et al*, 2012), and higher alcohol dependence severity mediated by neuroticism (Schwandt *et al*, 2013). Alcohol may be a means of coping with acute and chronic stressors, such as posttraumatic stress

disorder (PTSD), catastrophic events, and occupational stress (Crum *et al*, 1995; Keyes *et al*, 2012; Simpson *et al*, 2014).

This symposium brings together studies utilizing novel approaches to help improve our understanding of stress – past, acute and chronic - on alcohol seeking and consumption and related outcomes using a combination of human laboratory models, neuroimaging and clinical measures. The first three presentations are based on data from human laboratory studies that evaluate the effects of acute stress and alcohol cues on alcohol self-administration, both intravenous and oral. Stress cues employed in these studies include guided imagery scripts, negative mood induction and short-term abstinence, while alcohol cues included guided imagery scripts. The fourth presentation is based on data from a natural history and assessment study employing primarily self-report and clinical data on chronic early life stress. The studies provide distinct but complementary evidence highlighting the significant role of stress and its consequences with regard to alcohol seeking, consumption and its chronic consequences.

Examining factors that determine vulnerability as well as resilience to stress are of particular interest in the study of AUD because, in addition to increasing our understanding of the risk factors for AUD, such knowledge can be used to develop more effective treatments.

I. A novel human experimental model of stress-induced alcohol self-administration in binge and non-binge drinkers

The relationship between stress and alcohol use has been evidenced by numerous studies across various types of stressors. Craving for alcohol has been

shown to predict relapse in alcoholics (Bottlender and Soyka, 2004; Lovallo, 2006). Stress is a potent trigger for alcohol craving and subsequent relapse (Adinoff *et al*, 2005; Sinha, 2013; Sinha *et al*, 2011b). Studies show that craving and physiological responses to cues that mimic real-world alcohol and stress triggers can potentially elicit alcohol seeking behavior and has been predictive of relapse to alcohol use in alcohol-dependent individuals. However, the association between stress and alcohol cue reactivity, craving and subsequent alcohol consumption in non-dependent drinkers has been difficult to characterize. Laboratory studies of acute stress-induced craving for alcohol have used a variety of stressors including social stressors (Trier), personalized experiences (guided imagery scripts) and psychophysiological (fear-potentiated startle and shock) (de Wit *et al*, 2003; Hefner and Curtin, 2012; Kwako *et al*, 2015).

Very few studies have been conducted examining the effects of acute stress-induced alcohol self-administration, and most have used oral alcohol. Despite well-controlled experimental conditions, there can be an approximately 3-fold variance in the time course of breath alcohol concentration (BrAC) following doses of oral alcohol (Friel *et al*, 1995). We used an intravenous (IV) alcohol self-administration method (Stangl *et al*, 2016) that is based on a physiologically-based pharmacokinetic model for alcohol (Ramchandani *et al*, 1999). Our objective was to evaluate the influence of acute stress and alcohol-cue reactivity, using guided-imaging scripts, on craving and IV alcohol self-administration (IV-ASA) in non-dependent drinkers, as well as examine the effect of drinking history on this response by comparing binge and non-binge drinkers. Additionally, we wanted to explore potential effects from childhood trauma on stress response and self-administration in the sample.

Participants (N=25) were healthy non-dependent drinkers (21-45 years) that were stratified into two groups based on binge (N=14) or non-binge drinking patterns as measured by the Timeline followback (TLFB). Binge drinkers were required to have at least 2 binge-drinking episodes in the month prior to the study, and non-binge drinkers were required to have no binge-drinking episodes in the month prior to the study. A binge episode was defined as consuming at least 4 drinks for females and at least 5 drinks for males in that episode. Alcohol use and problems were quantified using the Alcohol Use Disorder Identification Test (AUDIT) (Babor *et al*, 1989), while the Structured Clinical Interview for DSM-IV diagnosis (First, 2002) was used to exclude individuals with alcohol use disorder. Each participant completed three experimental IV-ASA sessions using the Computer-assisted Alcohol Infusion System (CAIS). This provides individually standardized incremental increases in breath alcohol concentration (BrAC) that are identical across all participants. Each session began with an exposure to a 5 minute audio recording of a personalized guided-imagery script designed to induce an acute stress, an alcohol-craving, or a neutral-relaxing state that has been previously shown to reliably elicit alcohol craving (Sinha *et al*, 2011b). This was immediately followed by a 120 minute free-access IV-ASA session in which participants could push a button to receive standardized IV alcohol infusions, following an FR1 schedule (one button push = one infusion), as described in our previous work (Stangl *et al*, 2016). IV-ASA measures included peak and average estimated blood alcohol content (BAC), number of button presses and total ethanol (g) infused. Subjective measures of stress and craving included the Subjective Units of Distress Scale (SUDS), the Alcohol Urge Questionnaire (AUQ) and the Drug Effects Questionnaire (DEQ)

(Benjamin *et al*, 2010; Bohn *et al*, 1995; Fischman and Foltin, 1991). Serial blood samples were collected and assayed for cortisol (CORT) and adrenocorticotropic hormone (ACTH). Adverse childhood events were measured using the Childhood Trauma Questionnaire (CTQ) (Bernstein *et al*, 2003). All analyses covaried for gender.

[insert Table 1 here]

Table 1 lists the demographics and characteristics of participants in the study. Binge and non-binge drinkers did not differ significantly by age. As expected, binge drinkers had significantly higher AUDIT scores ($F=7.56$, $p=0.01$), as well as higher measures on the TLFB including total drinks in the past 90 days ($F=24.18$, $p<0.001$), total drinks per drinking day in the past 90 days ($F=29.48$, $p<0.001$), but were not significantly different for total drinking days in the past 90 days. Results demonstrated that the imagery scripts successfully induced reactivity for both binge and non-binge drinkers, with increases in SUDS score (p's<0.001) following the stress cue script compared with the neutral cue script. Comparison of measures of cue-reactivity, craving and IV-ASA between binge and non-binge drinkers revealed robust differences. Binge drinkers had greater IV-ASA following stress ($p<0.01$) and alcohol cues ($p<0.05$) compared to the neutral cue and also had greater peak and average BACs compared to the non-binge drinkers during the stress ($p<0.01$) and alcohol cue ($p<0.05$) exposure sessions. Binge drinkers had significantly higher craving post-script following both stress ($p<0.05$) and alcohol cues ($p<0.01$) compared to the neutral cue, while the non-binge drinkers showed no significant differences across cue type. Binge drinkers also craved alcohol more so than the non-bingers during the stress cue ($p<0.05$). Peak scores of "urge" for alcohol and "want more" alcohol were greater during the stress cue

in comparison to the neutral cue (all p's<0.05), and were also significantly higher in the binge drinking group compared to the non-binge drinking group (p's<0.01).

Peak ACTH levels following stress and alcohol cues were higher in binge-drinkers (all ps<0.05). During the stress cue session, peak CORT was positively associated with peak BAC and peak feelings of "high" as measured by the DEQ, but only in the bingers (r=0.78, p=0.013; r=0.79, p<0.01)). During the alcohol cue, peak CORT levels and peak urge for alcohol was positively associated with the binge drinking group, but not the non-bingers (r=0.68, p=0.013).

A preliminary examination of the effect of CTQ was explored in the sample. Seven binge drinkers were positive for CTQ (CTQ score in moderate to severe category) while only 3 non-binge drinkers were positive for CTQ. Due to the small sample size, we compared participants positive or negative for childhood trauma, irrespective of drinking history. Figure 1 illustrates the main findings of this analysis. Those positive for childhood trauma (N=10) had greater peak and average BAC during the stress cue session (all p's<0.05), and had greater scores for "want more" alcohol (p<0.01). However, when childhood trauma was controlled for in the earlier analyses comparing binge and non-binge drinkers, the significant differences between binge and non-binge drinkers on measures of IV-ASA, subjective response and neuroendocrine response remained.

[insert Figure 1 here]

These results are the first demonstration, to our knowledge, of stress-induced increases in IV-ASA in non-dependent binge drinkers. These data may provide important information on the relationship between stress and alcohol-seeking behavior

that may underlie risk for alcohol-related problems. Comparisons between binge and non-binge drinkers may provide important information on potential triggers for excessive alcohol use in this sample of non-dependent drinkers. This experimental model may serve as a translational tool to screen novel pharmacological agents that target brain stress systems in reducing drinking and relapse in AUD, particularly in alcoholics with anxious traits. Future studies will examine genetic and environmental influences on this stress-induced ASA behavior. In particular, we will look at childhood trauma in our larger non-dependent sample to determine its effect on free-access IV-ASA (without acute stress) during the session.

II. Binge-heavy alcohol alters cortisol and subjective craving: impact on implicit alcohol motivation and intake

As described in Section I, binge and heavy alcohol use above recommended levels may promote higher levels of motivation for alcohol and less control over alcohol use, thereby increasing risk of the development of Alcohol Use Disorders (Field *et al*, 2010; King *et al*, 2011; King *et al*, 2014). The effects of stress and alcohol cues are linked to alcohol's robust effects on the HPA axis and there is some evidence that these effects are seen prior to the development of AUDs (Blaine and Sinha, 2017). Additionally, alcohol intake directly affects the functioning of the HPA axis (Lee *et al*, 2004; Richardson *et al*, 2008), and may alter craving and cortisol levels differently in problem drinkers than social drinkers. While IV alcohol administration allows for tight control of breath alcohol levels, oral alcohol administration allows for a more ecologically valid assessment of behavioral alcohol motivation and intake. Therefore,

we conducted a human laboratory experiment to examine the effects of stress and alcohol cues on alcohol craving, cortisol levels, and implicit behavioral motivation to consume alcohol in non-dependent drinkers.

Twenty-six problem drinkers and 38 social drinkers (see Table 2) - participated in a laboratory challenge procedure during which they were exposed to 3 personalized 5-minute imagery conditions (stress, relaxing, and alcohol cue, described in Section I), followed by the "alcohol taste test" (ATT) as a measure of implicit alcohol motivation and intake, presented across 3 consecutive days, 1 per day in a randomized and counterbalanced order (Milivojevic *et al*, 2017). Participants were characterized as problem or social drinkers according to Alcohol Use Disorder Identification Test (AUDIT) scores (>8 problem drinker, <8 social drinker). Subjective measures of alcohol craving and blood plasma samples for cortisol levels were collected at several time-points: baseline, immediately following imagery exposure, immediately following discrete alcohol cue, immediately following the ATT, and every 15 minutes for an hour afterward. Multi-level linear mixed effect models examined craving and cortisol responses to imagery, cues, and alcohol consumption and whether these responses differed by group.

[insert Table 2 here]

A significant Group x Condition x Time-point interaction was observed for alcohol craving, $F(4, 494) = 3.2$, $p = 0.01$ (figure 2A,B). Problem drinkers reported higher craving in response to stress imagery exposure compared with the social drinkers ($p = 0.007$). Both groups reported significantly higher craving in the cue compared with the neutral condition immediately following imagery exposure (problem drinkers:

cue>neutral, $p < 0.0001$; social drinkers: cue>neutral, $p < 0.0001$), Problem drinkers also reported significantly elevated alcohol craving across all 3 imagery conditions in response to the presentation of beer, compared with the social drinkers (stress: $p = 0.003$; cue: $p = 0.02$; neutral: $p = 0.03$).

Additionally, in phase I, there was a significant Group x Timepoint interaction for the cortisol response to imagery and discrete cues, with the problem drinkers showing a blunted response relative to the social drinkers, $F(2, 481) = 7.3$, $p=.001$, (figure 2C). Following exposure to all 3 imagery conditions and a discrete alcohol cue, the problem drinkers consumed significantly more beer during the ATT compared with the social drinkers, $F(1, 62) = 11.5$, $p = 0.001$ (figure 2D).

[insert Figure 2 here]

The presented findings demonstrated how acute alcohol's stimulating effects involve activation of the HPA axis, but with binge drinking, neuroendocrine tolerance develops, resulting in higher basal sympathetic and blunted cortisol responses to alcohol and stress. This blunted phasic effect was associated with higher alcohol intake in problem drinkers, thereby also supporting the notion that such alcohol-related stress adaptations may contribute to higher alcohol motivation and intake. Other factors that may influence HPA axis response to alcohol include dose and drinking history. Doses of alcohol below 0.08 g% have been associated with a decreased HPA axis response in problem drinkers, but greater increases in those with lower to moderate levels of drinking history (Allen *et al*, 2011; Blaine *et al*, 2016; Waltman *et al*, 1993; Zimmermann *et al*, 2004). A recent study showed that those who are able to mount a high cortisol response to stress also showed an increased cortisol response to low doses of alcohol,

but report greater sedative effects with increasing doses of alcohol consumption, which correlates with increased cortisol responses at higher doses of alcohol (Brkic *et al*, 2016).

On the other hand, those who were low cortisol responders to stress showed a blunted cortisol response to acute alcohol and reported significantly less sedation at the highest alcohol dose. The subjective stimulant response to acute alcohol is also blunted by a greater recent drinking history, regardless of family history (Ramchandani *et al*, 2002a). This blunted stimulant response is also related to greater acute tolerance to alcohol and thus may contribute to greater consumption (Ramchandani *et al*, 2002b). King and colleagues (King *et al*, 2006; King *et al*, 2014) demonstrated in a series of longitudinal studies that problem drinkers who experience high stimulation in response to alcohol consumption go on to develop AUDs, whereas those drinkers who experienced sedative effects of alcohol continued to consume at low levels (King *et al*, 2015; King *et al*, 2006). Therefore, we suggest that BH drinkers may be drinking greater amounts of alcohol to normalize their HPA axis dysregulation (evidenced by an upregulated basal state and downregulated response to alcohol), similar to those with severe AUDs (Sinha *et al*, 2011a).

Finally, while this study was not powered to explore the role of gender or childhood trauma, we recognize both play an important role in the risk for developing AUDs and these variables should be examined in future studies. Nevertheless, our findings add to the clinical literature that suggest alterations in peripheral cortisol release in binge drinking has a direct effect on behavioral motivation to consumed

alcohol and thus may be a contributing mechanism underlying the development of AUDs.

III. Sex Differences in How Stress Affects Intravenous Alcohol Administration

Alcohol Use Disorders (AUDs) and stress have long been clinically, experimentally, and theoretically linked. Importantly, sex differences in the response to stress, alcohol, and related conditions are routinely reported in the literature (Becker *et al*, 2012). Clinically, substance use disorders have been consistently found to be more common in those conditions with altered stress systems including post-traumatic stress disorder, anxiety disorders, and depression (Boden and Fergusson, 2011; Debell *et al*, 2014; Jacobsen *et al*, 2001; Regier *et al*, 1990). Interestingly, those conditions are more commonly diagnosed in women while substance use disorders are more commonly reported in men (Breslau *et al*, 1997; Kessler *et al*, 2005). Similarly, stress induction laboratory paradigms have routinely been shown to be efficacious across a variety of domains, and sex-related differences in response to stress are routinely reported (Chaplin *et al*, 2008; Higley *et al*, 2011; Kirschbaum *et al*, 1992; Sinha *et al*, 1999).

Laboratory alcohol self-administration (ASA) is a method used to examine human consumption behavior in a controlled setting using one of two basic designs - Free-Access (FA) and Progressive-Ratio (PR). In common FA paradigms, subjects may consume as much alcohol as they desire in a specified interval, subject to safety constraints placed upon that consumption. Progressive-ratio (PR) paradigms require an ad-lib, increasing response or 'work' requirement to self-administer alcohol, and are designed to quantify the motivation for a specific reward. In this presentation, we

contrasted sex differences in human laboratory ASA after 2 distinct stress-inducing experiences – negative mood induction and monitored abstinence.

Each experiment used the Computer Assisted Alcohol Infusion System (CAIS, (Plawecki *et al*, 2013; Zimmermann *et al*, 2009; Zimmermann *et al*, 2008)) to deliver identical incremental changes in BrAC or saline infusions as rewards within PR designs (Plawecki *et al*, 2013). During the ASA interval, subjects were required to perform a predefined and exponentially increasing number of Constant Attention Task (CAT) trials per work set for each successive alcohol or saline reward with progress tracked separately. The CAT is an effortful adaptive task of cognitive skill that minimizes effects of practice, fatigue, and/or intoxication (Plawecki *et al*, 2013). Each work set, and each individual CAT trial, is initiated by the subject; participants were told that they could self-administer as much or as little as they desired, but that the session length would remain unchanged and discharge would not occur until 6-7pm or their BrAC was below 20 mg/dL, whichever was later. In the first experiment, we examined operant responding for alcohol after a negative mood-induction priming exercise. In the second, we examined motivation for alcohol after a period of monitored abstinence was explored. In each, the cumulative work for alcohol rewards (CWA) is the primary outcome variable, defined as the sum total of all CAT trials completed during the session.

Experiment 1: Negative Mood Induction

Research has long supported the bidirectional association between negative mood and alcohol use. Specifically, a commonly reported motive for drinking alcohol is to regulate a negative mood (Cooper *et al*, 1995) and negative moods induce alcohol craving (Litt and Cooney, 1999). While consistent differences in alcohol use patterns

and problems have been reported across men and women, the etiology of those differences remains unclear. The objective of the larger study was to assess how negative mood induction, compared to a neutral mood induction, altered alcohol seeking and consumptive behavior (Cyders *et al*, 2016) using the CAIS PR paradigm.

Participants aged 21-25 years were recruited from the community. Inclusion/exclusion criteria comprised: current heavy alcohol users (consumed at least 7 drinks and at least one binge episode per week), good health, no past/present alcohol dependence, not currently pregnant or intending to become pregnant, or breastfeeding. Twenty subjects, ten women, completed the PR experiment. Women reported 6.4 +/- 1.3 drinks/drinking day and had AUDIT scores of 11.8 +/- 0.86 while the men consumed 5.2 +/- 1.5 Drinks/DD with AUDIT scores of 9.9 +/- 1.1. There were no statistically different demographic differences by sex.

The experiment consisted of 2, counterbalanced IV ASA sessions including negative versus neutral mood induction. Subjects completed either a FA or PR design, with only PR ASA outcomes discussed herein. The Life Events Narratives (Abele, 1990) were used to induce, and the Musical Mood Induction Procedure (Västfjäll, 2001) to maintain, either a negative or neutral mood. Each session was 2.5 hours long, consisting of a 15 mg/dL alcohol prime over 10 minutes and then a 2 hour ASA interval beginning approximately 10-15 minutes later. Between the intervals, subjects listened to music and read their life narrative aloud. The alcohol reward comprised a 7.5 mg/dL linear increase in BrAC from its current value over 2.5 minutes followed by a linear descent of -1.0 mg/dL until the next alcohol reward. A 120 mg/dL BrAC safety limit was specified, precluding any administration that would result in exposures above that level.

The mood induction procedures were successful and altered ASA, with differential impact by sex. Across the entire experimental sample, negative mood induction was associated with a decrease in self-reported mood (mean change=-1.85 (SD=1.72), t(32)=-6.81, p<.001). Overall, CWA was reduced in the negative versus neutral session (F=5.45, p=.03; partial η^2=0.24). Women and men demonstrated significantly different CWA during the negative mood session, with women reducing their motivation for alcohol in the negative versus neutral session while men maintained their effort (Figure 3). (See Cyders et al 2016 for complete discussion of results.)

[insert Figure 3 here]

Experiment 2: Human Post Abstinence Response

The alcohol deprivation effect (ADE), or the change in alcohol consumption after a period of forced abstinence, is a well-studied preclinical phenomenon. Notably, the ADE has been associated with the high alcohol preferring animal lines and has been associated with an escalating effect of repeated abstinence intervals (Bell *et al*, 2004; McKinzie *et al*, 1998; Rodd-Henricks *et al*, 2000; Spanagel and Holter, 1999). The premise of this experiment is that abstinence from alcohol is likely to change the motivation for alcohol upon resumption; a Post-Abstinence Response (PAR). Evidence of a PAR effect in humans is limited and indirect. Craving has been reported to increase with repeated detoxifications in those with severe alcohol use disorder (Hillemacher *et al*, 2006; Malcolm *et al*, 2000a; Malcolm *et al*, 2000b). Additionally, the increase in and pattern of alcohol drinking over the college years may also reflect a PAR phenomenon (Brown *et al*, 2008; Del Boca *et al*, 2004; Hartzler and Fromme, 2003; O'Connor and Colder, 2005; O'Hare, 1990; White *et al*, 2006). Direct experimental evidence of such a

phenomenon is extremely limited. Recently, McCaul and colleagues reported alterations in alcohol related responding in 30 non-treatment seeking subjects with an AUD, after a 4-day detoxification +/- stress. The Trier Social Stress Test or a neutral task was administered before a simple button press PR session for alcohol or monetary rewards delivered later. Stress increased alcohol response rate and decreased reward changeovers but direct examination of the impact of abstinence versus baseline alcohol responding was not reported (McCaul *et al*, 2017). The specific objective of the current study was to determine if a PAR effect exists in humans. We hypothesized that an abstinence effect would be identifiable and in humans and should be associated with known AUD risk factors; please see Plawecki et al (Plawecki *et al*, 2017) for a complete discussion.

Participants were heavy drinkers recruited from the community. Inclusion criteria comprised: age 21-30, heavy alcohol users (at least 14/7 drinks per week for men/women), good health, no current AUD or physical dependence precluding unmonitored abstinence, not currently/intending to become pregnant or breastfeeding. Binge drinking was defined as 4/5 drinks in an episode for women/men (Keyes *et al*, 2012). Fifty-two subjects (24 female) completed the protocol. Women consumed 3.9 +/- 0.3 drinks/drinking day and men consumed 5.7 +/- 0.5 drinks/drinking day ($p < 0.01$), but there were no significant differences when normalized to exposure (gram alcohol per total body water per drinking day). Men had AUDIT scores of 11.9 +/- 0.8 while the women had scores of 10.5 +/- 0.5 ($p=0.1$). There were no statistically different differences in binge drinking or family history of alcoholism density related to sex.

The experiment comprised 2, counterbalanced IV ASA sessions in each subject's usual vs. post-abstinence drinking conditions. Abstinence from alcohol lasted precisely 2 weeks and was monitored by a transdermal alcohol-sensing device, with data reviewed during a lab visit every 3-4 days. The Clinical Institute Withdrawal Assessment of Alcohol Scale – Revised (Sullivan *et al*, 1989) was also obtained during each abstinence interval visit and any score ≥8 would have led to dismissal and treatment referral. Each laboratory session was 2.5 hours long, consisting solely of an ASA interval using the CAIS PR paradigm. After the completion of each work set, the participant's video monitor notified him/her to wait for the completion of reward delivery before another work-set could be initiated. Each alcohol reward provided a 12.5 mg/dL linear increase in BrAC from its current value over 2.5 minutes followed by a linear descent of -0.5 mg/dL until the next alcohol reward. A 150 mg/dL BrAC safety limit was specified for this experiment. In order to not interfere with their work for alcohol or the alternative reward, subjects responded to subjective response questions using a computerized visual analog scale as implemented in our past studies (Kosobud *et al*, 2015; Wetherill *et al*, 2012).

PAR was calculated as the change between cumulative work for alcohol rewards (CWA, consistent with study 1) during Usual drinking habits and upon Resumption from abstinence normalized by the average response, and expressed in percent. Two weeks of abstinence altered subjectively reported baseline craving for alcohol and resulted in sex associated ASA behavior differences. Craving increased from the Usual to the Resumption session ($p<0.01$), but without sex related differences. There was not a significant PAR across the entire population, but sex accounted for a significant

difference in the PAR distribution (Figure 4) (p <0.05 for sex group means). Females worked more for alcohol after 2 weeks of abstinence, +11.6 ± 12.1 %, compared to males, who decreased by -23.9 ± 14.4 %.

[insert Figure 4 here]

Summary

The relationship between stress and alcohol is bi-directional and complex. In this presentation, we reported the results of two human stress induction experimental paradigms on motivated work for alcohol. In experiment 1, sex differences in CWA were exacerbated by negative affect, with women tending to reduce their responding. In experiment 2, men reduced their CWA while women tended to increase it in the context of abstinence. Taken together, our results suggest sex differences in alcohol seeking appear to depend on the type of stressor. The wider human literature supports this observation, with reports that suggest sex differences in stress response vary by induction procedure, outcome measure, and potentially modulating factors (Stroud *et al*, 2002){Kirschbaum, 1995 #570}{Kelly, 2008 #569}{Chaplin, 2008 #572}{Li, 2005 #571}. Further complicating interpretation is significant variance in reported sex differences within similar constructs. For example, the relationship between negative affect as well as depressive symptoms and alcohol consumption has been shown to be stronger, weaker, and not different between men and women {Aneshensel, 1983 #573}{Hussong, 2001 #574}{Hartka, 1991 #575} . Similarly, sex differences in craving as a response to stress have been reported across multiple substance (for example {Conner, 2009 #576}{Weinberger, 2012 #577}{Saladin, 2012 #578}{Rubonis, 1994 #579}). Consequently, interactions between the stress type, sex, and alcohol seeking behavior

warrants further exploration and comparisons across experiments 1, 2, and the symposium should be made carefully.

IV. Childhood trauma in alcohol dependence: vulnerability and relative resilience to early stress exposure

In our efforts to understand the effects of stress on alcohol consumption and the development of alcohol use disorder, it is important to consider not only current stress exposure, but past stressors as well. This is particularly true for events occurring early in life – childhood stress and trauma has been repeatedly shown to leave a lasting signature on the brain and body (De Bellis *et al*, 2014; McEwen *et al*, 2015). The association between childhood trauma and risk for developing an alcohol use disorder has been well documented (De Bellis, 2002; Enoch, 2011; Huang *et al*, 2012; Lotzin *et al*, 2016; Schwandt *et al*, 2013). However, the fact that 1) not all individuals exposed to early life trauma go on to develop alcohol-related problems, and 2) the range and severity of alcohol-related problems differs substantially among trauma-exposed individuals, suggests a more complex story encompassing both vulnerability and resilience.

Resilience is generally defined as the process of adapting well in the face of significant adversity, trauma, tragedy, or stress (Yehuda *et al*, 2006). Resilience can be attributed to individual traits that serve as protective factors when faced with adversity, or to individual characteristics and coping mechanisms that develop in reaction to adversity; more than likely, it is a combination of both. Resilience is also often multidimensional, in that individuals may adapt well in some domains but exhibit

problems in others (Luthar *et al*, 2000). This latter point has particular relevance for alcohol dependence, as it is a multidimensional and heterogeneous disorder (Hesselbrock and Hesselbrock, 2006). It is important to consider the multiple domains that may reflect vulnerability and/or resilience in the face of childhood trauma exposure, in order to gain a better understanding of how the negative consequences of adversity might be reduced or minimized.

In previous work, we have shown that childhood abuse and neglect are linked to increased risk for severe alcohol dependence and psychiatric comorbidity (Huang *et al*, 2012; Schwandt *et al*, 2013). Stemming from this work, and from continued exploration of the effects of childhood trauma, we have also identified a subgroup of individuals exposed to significant childhood trauma who have only mild alcohol-related problems, or none at all. Utilizing the Childhood Trauma Questionnaire (CTQ), which has been validated in both community and substance abuse samples (Bernstein *et al*, 2003; Thombs *et al*, 2007), we focused on subjects who scored in the upper quartile (≥46) for the total score on the CTQ. Out of a total of 1472 subjects who completed the questionnaire, 367 were found to fall into this range (Table 3). In our first approach to analyzing this sample, we identified three smaller subgroups based on severity of alcohol dependence: vulnerable (VN, n=67) subjects had severe AD (≥27 on the Alcohol Dependence Scale (Skinner and Allen, 1982), moderately resilient (MR, n=64) subjects had less severe AD (≤17 on the ADS), and resilient (RS, n=63) subjects were non-alcohol dependent (figure 5).

[insert Table 3 here]

[insert Figure 5 here]

Having identified two relatively "resilient" subgroups in the trauma sample, we compared them to the vulnerable subgroup on a variety of domains (unpublished data). We first looked at the subtypes of childhood trauma reported, and found that subjects in both resilient groups (MR and RS) scored lower on two of the abuse subscales of the CTQ, emotional abuse and sexual abuse. After controlling for these differences in trauma subtype, we also found that MR and RS subjects scored significantly lower on personality measures of neuroticism, impulsivity, and aggression, compared to the VN group. Subjects in the RS group scored significantly lower on trait anxiety, and on state-dependent ratings of anxiety and depression, compared to both the MR and VN groups. Lastly, family history density of alcohol problems was significantly lower in both the MR and RS groups.

We recognize, however, that this approach is limited by the fact that subgroups are determined based on a single measure – alcohol dependence severity. As stated previously, the concept of resilience is multidimensional and is best understood by considering the various domains that characterize individuals. Therefore, we adopted a second, more data-driven approach where we identified subgroups based on Latent Class Analysis (LCA). This has the advantage over the previous approach in that it is a multivariate technique, defining subgroups based on multiple measures including both continuous and categorical outcomes. Furthermore, it utilizes the full trauma sample (n = 367) in determining subgroups, whereas before only smaller subgroups were described based on alcohol dependence severity. The variables used as indicators in the LCA included the subscales of the CTQ, a measure of early life stressful events, personality factors, impulsivity and aggression measures, negative affect, and family

history of alcohol use problems (see Table 4 for individual measures). Analysis was conducted using Latent Gold (Statistical Innovations, Belmont, MA), and based on the Bayesian information criterion a three-class solution was found to best fit the data (BIC = 36853.59; BIC for 1-, 2-, and 4-class solutions were 37675.03, 37342.78, and 36960.99, respectively). Class information and summary statistics for each of the indicator variables in each class are presented in Table 4. Pairwise comparisons for significant differences were based on analysis of variance with Tukey post-hoc tests of the measures (Chi-square test was used for gender) by class assigned by LCA.

[insert Table 4 here]

Class 1 represented the largest group (n = 178, 48%), and was characterized by intermediate values for many of the measures tested, the exceptions being gender (highest proportion of females), sexual abuse (essentially absent in this group), and emotional neglect (highest level in all three groups). Class 2 (n = 136, 38%) was the oldest, had the highest levels of early life stressful events, sexual abuse, neuroticism, anxiety and depression symptoms, and family history of alcohol use problems. Class 3 was the smallest (n = 53, %14), was the youngest, had the lowest levels of early life stressful events, emotional abuse, neuroticism, impulsivity, aggression, trait anxiety, anxiety and depression symptoms, and family history, as well as the highest level of conscientiousness. Notably, Class 3 was characterized by a moderate to severe level of exposure to sexual abuse (whereas sexual abuse was nearly absent in Class 1). As the final step, we investigated whether class membership subsequently predicted alcohol-related problems and psychiatry comorbidity (Table 5). Controlling for age and gender, we found that class membership significantly predicted alcohol dependence severity,

consumption, and lifetime diagnoses of alcohol dependence, other substance dependence, mood, and anxiety disorders. Taken together, these results point to Class 3 as the “Resilient” class, and Class 2 as the “Vulnerable” class.

[insert Table 5 here]

Our results suggest that there is heterogeneity among childhood trauma-exposed individuals in terms of personality and negative affect, and that these differences may mitigate the relationship between severe childhood trauma exposure and risk for alcohol dependence, as well as other psychiatric disorders, later in life. Group differences in family history of alcohol problems suggest a potential genetic component to this relative resilience in trauma-exposed individuals. We note, however, that the current study has several limitations. First, the question remains as to whether the characteristics linked to resilience in this study are precursors to, or consequences of, the development of alcohol use problems. Possibly it is a combination of both. Second, we lack data on cognitive, environmental, and coping-related measures related to resilience. Plans are already in place to capture more data in these domains. Future analyses are also planned to consider measures of brain structure and function, genetic variation, and epigenetic modifications.

In conclusion, we reiterate that it is just as important, if not more so, to look at factors contributing to resilience in the face of early childhood adversity, as it is to look at factors conferring risk or vulnerability. The challenge remains in translating knowledge of these sources of resilience into therapies for prevention and treatment of medical and psychiatric disorders in adulthood. McEwen and colleagues (McEwen *et al*, 2015) advise that while interventions cannot necessarily reverse the effects of trauma

during development, they may assist in providing compensatory mechanisms that can minimize the effects of trauma. These interventions will likely involve a combination of pharmaceutical, behavioral, and environmental interventions, as reflected in the multidimensional nature of resilience.

Discussion

Like the two-faced Roman god Janus, stress and reward represent two aspects of alcohol seeking behavior. On the one hand, alcohol is anxiolytic which relieves stress associated with abstinence after heavy drinking, resulting in motivation to resume drinking. On the other hand, alcohol act as a stressor, activating the hypothalamic-pituitary-adrenal (HPA) axis resulting in the release of Corticotropin-Releasing Factor (CRF), ACTH, and glucocorticoids that affect the reward circuitry and may play a role in escalation of alcohol consumption (Becker, 2012).

The studies summarized above were all performed in human subjects, providing an opportunity to examine stress and alcohol effects in the context of the extensive preclinical data and to facilitate cross-species extrapolation. The study by Stangl and colleagues demonstrated, for the first time, that stress and alcohol cues increased alcohol self-administration in non-dependent binge drinkers, compared to the neutral cue, and also that binge drinkers had greater peak and average BACs compared to the non-binge drinkers during the stress and alcohol cue exposure sessions. Furthermore, binge drinkers also craved alcohol more so than the non-bingers during the stress cue. In experimental animal studies, Koob (Koob, 2013) reported that the activation of the HPA axis drives alcohol-seeking behavior through negative reinforcement mechanisms.

Conversely, binge-like ethanol exposure of experimental animals resulted in the engagement of the CRF signaling in the extended amygdala resulting in increased alcohol drinking (Cui *et al*, 2013). The extended amygdala is involved in increased alcohol consumption associated with repeated alcohol exposure and withdrawal (Koob, 2008), and gate binge-like drinking in rodents (Lowery-Gionta *et al*, 2012). It is important to note that when the HPA axis is dysregulated, due to any reason, changes in cortisol reactivity is associated with progression to alcoholism risk (Stephens and Wand, 2012). Non-alcohol-dependent drinkers could be at risk of developing alcoholism because of their drinking pattern or because of their genetic background.

It has been suggested that glucocorticoids, especially cortisol may be involved in uncontrolled drinking (Stephens and Wand, 2012). The study reported above by Blaine and colleagues demonstrated that glucocorticoid response to stress drives compulsive alcohol motivation and intake in binge/heavy drinkers. One important action of cortisol is its effects on learning and memory, especially emotionally charged memory and habit learning (van Stegeren *et al*, 2010). Also, in experimental animals, cortisol exhibited reinforcing properties that modulate self-administration of alcohol (Piazza and Le Moal, 1997).

Plawecki and colleagues presented data examining gender differences in the effect of two distinct stress paradigms, and reported that gender differences in alcohol seeking behavior appear to depend on the type of stressor. Using functional magnetic resonance imaging, a study investigated the neural correlates of stress and alcohol context cue experiences and examined sex differences in these responses. Sex differences reported in neural processing of stress and alcohol-cue experiences have

implications for sex-specific vulnerabilities to stress- and alcohol-related psychiatric disorders (Seo *et al*, 2011).

Finally, novel clinical data reported by Schwandt and colleagues provided a new perspective on the relationship between childhood trauma and AUD by suggesting possible underlying mechanisms that confer resilience, rather than vulnerability. An earlier study reported that childhood trauma may sensitize stress-response systems, and predicts drinking severity in alcohol-dependent men (Eames *et al*, 2014). Factors involved in excessive alcohol consumption including vulnerability or resilience to stress are of great relevance to AUD because such knowledge can be used to develop more effective treatments. Research suggests that the HPA axis may offer useful targets for pharmacotherapy of alcoholism (Higley *et al*, 2012).

Needless to say, the role of the HPA axis in alcohol consumption is only one aspect among the varying repertoire of factors that influence the uncontrolled alcohol intake, including but not limited to, CRF, Dynorphin, NPY, Oxytocin, vasopressin, nociception, glucocorticoids, mineralocorticoids, ANS, endocannabinoids, integration of the circadian and stress systems, neuroendocrine system, CCK, neurotransmitters, etc. Finally, the interaction between comorbid conditions such as depression, PTSD, anxiety, dysphoria, depression, and stress with alcohol consumption need to be addressed.

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Table 1. Demographics and characteristics of participants in Study I (Stangl).

	Non-Binge Drinkers, N=11	Binge Drinkers, N=14
AUDIT score	4.0 (1.90)	6.31 (2.62)
Age	27.91 (6.66)	26.10 (4.93)
Years of education	16.81 (5.47)	16.85 (1.87)
Gender--% males	54.5%	50%
Race (%)		
Caucasian	54.5%	50.0%
African American	45.5%	21.4%
Hispanic	0	14.3%
Asian	0	7.1%
Other	0	7.1%
No. Drinks in past 90 days	40.54 (27.41)	102.81 (40.57)
No. Drinks per drinking day in past 90 days	1.78 (0.037)	3.63 (1.23)
No. meeting criteria for current/past mood disorder	0	0
Childhood Trauma Positive	N=3	N=7

*: Values presented as mean (std. deviation). Shaded area: $p<0.05$

Table 2. Demographics and characteristics of participants in Study II (Blaine).

	Social Drinkers, N=38	Problem Drinkers, N=26
AUDIT score	4.1 (5.0)	13.6 (4.2)
Age	30.1 (7.9)	27.2 (6.8)
Years of education	15.5 (1.7)	16.0 (2.3)
Gender--% males	68.4% (n=26)	80.8% (n=21)
Race (%)		
Caucasian	63.1%	80.8%
African American	21.1%	11.5%
Hispanic	5.3%	0
Asian	7.9%	3.8%
Other	2.6%	3.8%
No. years drinking	5.3 (5.0)	8.5 (6.5)
No. drinks in past month	24.0 (25.7)	82.5 (71.8)
No. smokers	1	2
No. meeting criteria for lifetime mood disorder	3	1
No. meeting criteria for current mood disorder	1	0
No. meeting criteria for lifetime anxiety disorder	1	0
No. meeting criteria for current anxiety disorder	0	0

*: Values presented as mean (std. deviation). Shaded area: $p<0.05$

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Table 3. Sample Characteristics of participants in Study IV (Schwandt)

Measure	Trauma Sample (n = 367)
Gender	213 Males (58%) 154 Females (42%)
Race	134 White (37%) 197 Black (53%) 36 Other[1] (10%)
Age (mean, standard deviation)	42.1 (11.1)
Education (Years)	13.6 (3.6)
Early Life Stressful Events[2]	5.7 (3.1)
CTQ Total Score	61.6 (14.3)
Emotional Abuse	14.4 (4.8)
Physical Abuse	11.8 (5.0)
Sexual Abuse	10 (7.0)
Emotional Neglect	15.1 (4.5)
Physical Neglect	10.3 (4.2)
Heavy Drinking Days[3]	54.0 (33.1)
Avg. Drinks Per Drinking Day[3]	12.0 (8.7)
Alcohol Dependence Severity	19.7 (9.9)
Family History Density[4]	0.2 (0.2)
Neuroticism[5]	58.3 (11.2)
Extraversion[5]	50.1 (10.3)
Openness[5]	51.5 (10.2)
Agreeableness[5]	44.1 (11.0)
Conscientiousness[5]	44.9 (12.0)
Impulsivity[6]	68.9 (13.2)
Aggression[7]	100.9 (21.3)
Spielberger Trait Anxiety	46.2 (12.4)
Brief Scale for Anxiety	10.3 (7.8)
Montgomery-Asberg Depression Rating Scale	13.5 (10.1)

[1] Includes 8 Asian, 4 American Indian/Alaskan Native, 11 Multiracial, and 13 Unknown
[2] From the Early Life Stress Questionnaire (ELSQ)
[3] From the Timeline Followback (TLFB, 90 days)
[4] Family Tree Questionnaire (FTQ): the proportion of first- and second-degree relatives with a known alcohol use problem
[5] NEO Five Factor Personality Inventory-Revised
[6] Barratt's Impulsivity Scale (BIS)
[7] Buss-Perry Aggression Questionnaire (BPAQ)

Table 4. Latent Class Analysis Results – Three Class Solution

Measure	Class1	Class 2	Class 3	Wald Test p-value
Percent of Sample	48% (178)	38% (136)	14% (53)	
Demographics				
Gender (% Female) [1,2]	73%	42%	49%	<0.0001
Age[3]	41.8	43.7	38.9	0.04
Childhood Stress/Trauma				
Early Life Events[1, 2, 3]	5.3	6.7	4.2	<0.0001
Emotional Abuse	14.8	14.5	13.0	0.07
Physical Abuse	11.7	12.2	10.9	0.25
Sexual Abuse[1, 2, 3]	5.0	16.2	10.4	<0.0001
Emotional Neglect[1]	15.8	14.3	14.5	0.01
Physical Neglect	10.7	10.1	9.3	0.06
Personality				
Neuroticism[1, 2, 3]	58.5	61.8	49.0	<0.0001
Extraversion	49.8	51.5	48.0	0.10
Openness	51.1	51.0	54.3	0.11
Agreeableness	43.8	44.1	44.9	0.85
Conscientiousness[2, 3]	44.2	42.3	53.6	<0.0001
Impulsivity[2, 3]	70.2	72.4	55.0	<0.0001
Aggression[2, 3]	102.2	104.8	85.9	<0.0001
Negative Affect				
STAI Trait Anxiety[2, 3]	49.2	50.9	32.2	<0.0001
CPRS Anxiety Symptoms[1, 2, 3]	10.9	12.9	0.4	<0.0001
CPRS Depression Symptoms[2, 3]	14.6	16.6	0.5	<0.0001
Family History Density[1, 2, 3]	0.17	0.24	0.06	<0.0001

[1]Class 1 different from Class 2; [2]Class 1 different from Class 3; [3]Class 2 different from Class 3. Pairwise comparisons based on analysis of variance of measures by class assignment obtained from latent class analysis (see text).

Table 5. Class Membership Predicts Alcohol-Related Outcomes and Psychiatric Comorbidity

Measure	Class 1	Class 2	Class 3		
	Mean (SD)	Mean (SD)	Mean (SD)	F[1]	p
Alcohol Dependence Severity	19.78 (8.94)	23.11 (8.48)	4.01 (8.38)	56.38	<0.0001
Heavy Drinking Days	56.23 (32.65)	59.72 (31.07)	27.19 (30.99)	22.0	<0.0001
Average Drinks/Drinking Day	12.0 (8.40)	13.90 (7.98)	4.72 (7.95)	25.13	<0.0001
	Odds Ratio (95% C.I.)	Odds Ratio (95% C.I.)	Odds Ratio (95% C.I.)	Wald Chi-Square[2]	p
Lifetime Alcohol Dependence	reference	2.51 (0.90, 7.00)	0.08 (0.04, 0.18)	57.41	<0.0001
Lifetime Mood Disorder	reference	1.65 (0.99, 2.74)	0.41 (0.18, 0.99)	11.53	0.003
Lifetime Major Depression	reference	1.75 (1.04, 2.95)	0.05 (0.22, 1.18)	9.99	0.007
Lifetime Anxiety Disorder	reference	2.08 (1.26, 3.43)	0.22 (0.09, 0.51)	28.27	<0.0001
Lifetime PTSD	reference	2.89 (1.71, 4.88)	0.28 (0.10, 0.77)	29.17	<0.0001
Lifetime Substance Use Disorder	reference	1.56 (0.93, 2.61)	0.15 (0.06, 0.33)	29.29	<0.0001

[1] Analysis of Covariance (ANCOVA), controlling for age and gender
[2] Logistic Regression, with Class 1 as the reference group, controlling for age and gender

Figure 1. Childhood Trauma and Stress-Cue Exposure

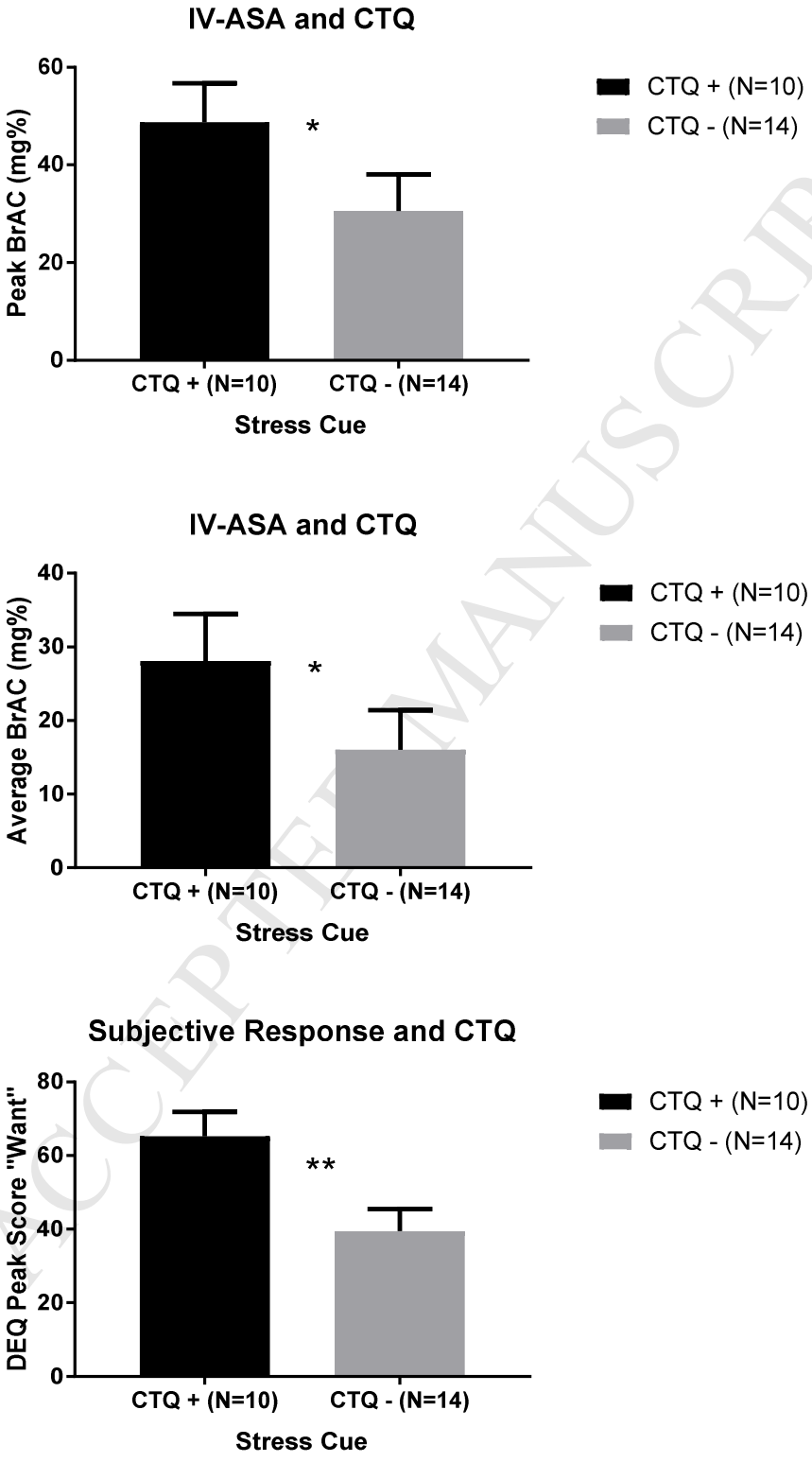


Figure 2. Alcohol craving in (A) social drinkers and (B) problem drinkers as a function of timepoint. (C) (D) Problem drinkers consumed higher amounts of beer following presentation of beer cues compared to social drinkers in response to all 3 imagery conditions. Values are displayed as mean +/- SEM.

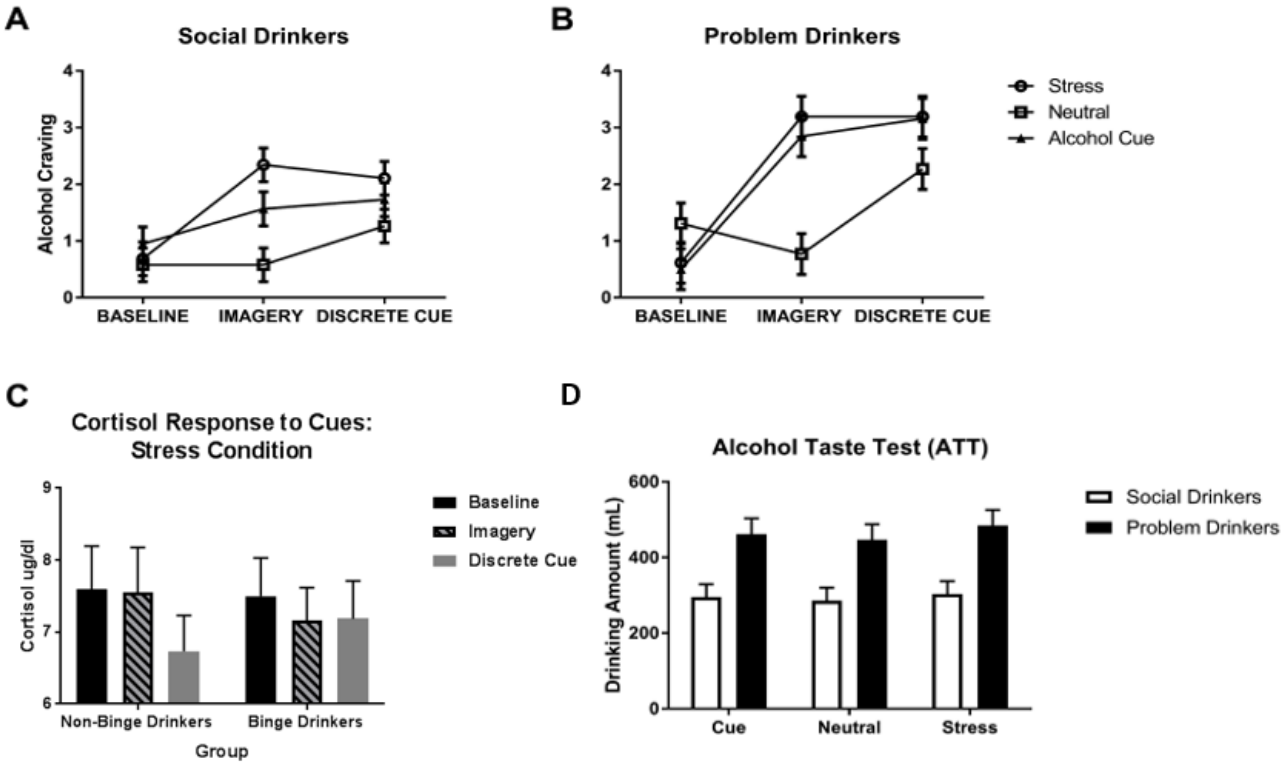


Figure 3: Cumulative Work for Alcohol in the Neutral and Negative Mood Sessions by Gender. Women worked less for alcohol in both sessions, compared to men, and the reduction for women was statistically significant in the negative mood session. See Cyders at al 2016 for more details.

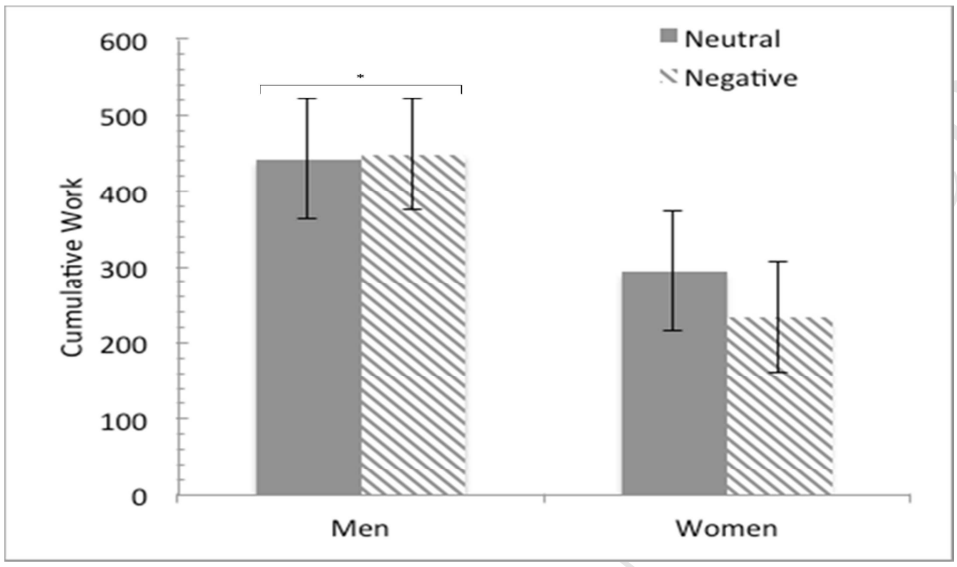


Figure 4: PAR based on Cumulative Work for Alcohol for Men and Women. Women tended to increase, while men decreased, their motivation for alcohol post abstinence. See Plawecki et al 2017 for more details.

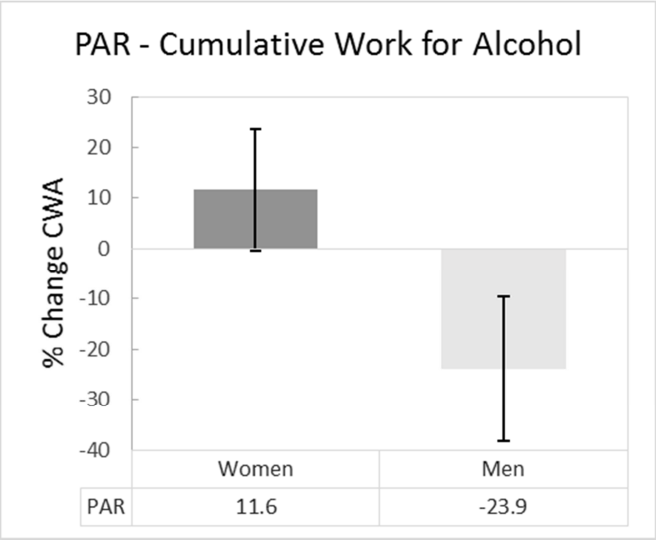
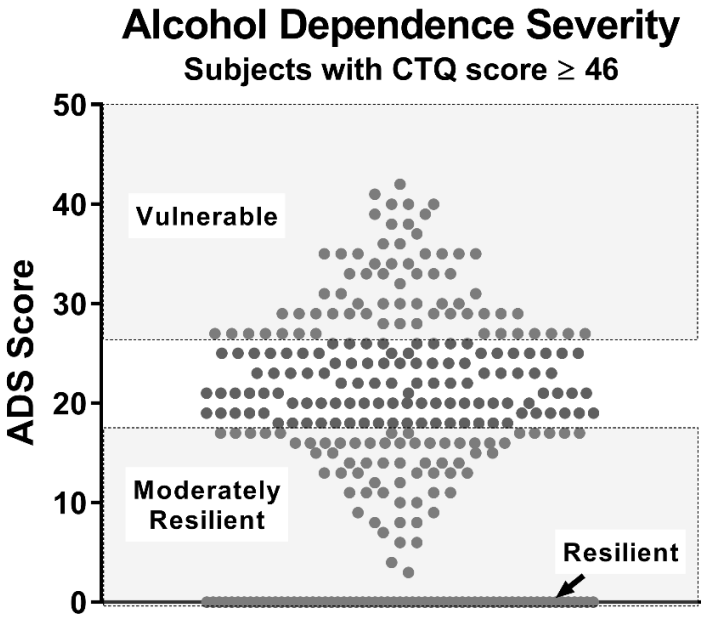


Figure 5. Distribution of the alcohol dependence severity score from the ADS in the high childhood trauma sample (n = 367), showing the three subgroups identified based on high severity (ADS score ≥27 = Vulnerable), low severity (ADS score ≤17 = Moderately Resilient), and absence of alcohol dependence (ADS of 0 = Resilient).



STRESS VULNERABILITY AND ALCOHOL USE AND CONSEQUENCES: FROM HUMAN LABORATORY STUDIES TO CLINICAL OUTCOMES

HIGHLIGHTS

- Acute stress cues increase craving and subsequent intravenous alcohol self-administration in non-dependent binge drinkers.
- Glucocorticoid response to acute stress cues drives compulsive alcohol motivation and intake in binge/heavy drinkers.
- Distinct gender differences in impact of stress paradigms on intravenous alcohol self-administration: negative mood induction may be associated with lower alcohol self-administration in women, while short-term abstinence may be associated with lower alcohol self-administration in men.
- Heterogeneity in personality and negative affect factors among childhood trauma-exposed individuals may drive risk or resilience to the development of alcohol use disorder.